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### III. REMARKS

Applicants respectfully request that this application be reconsidered in view of the above amendments and the following remarks.

#### 1. Status of the Claims

Claims 74-83 are pending in the application. The Examiner has withdrawn Claims 75-77 and 79 from consideration as drawn to a non-elected species. Accordingly, upon entry of the above amendments, Claims 74, 78 and 80-83 are pending for examination on the merits.

Pursuant to 37 C.F.R. §141, if a generic claim is found allowable, Applicants respectfully request consideration of the withdrawn claims which are written in dependent form or otherwise include all the limitations of the allowed generic claim. (Should a generic claim be found allowable, the withdrawn claims will be amended to encompass the limitations of the allowed generic claim.)

#### 2. Amendments to the Claims

Claims 74 has been amended to delete homodimers of formula (v).

Claim 83 has been amended as suggested by the Examiner in the January 15, 2003 Office Action to overcome improper form.

No new matter has been added.

Entry of this amendment is earnestly solicited.

Pursuant to the Official Gazette Notice dated February 25, 2003, entitled *AMENDMENTS IN A REVISED FORMAT NOW PERMITTED*, Applicants respectfully request that the provisions of 37 C.F.R. §1.121 be waived for the present amendments since these amendments are believed to comply with the revised amendment format set forth in the OG announcement.

#### 3. Claim Objections

Claim 83 has been objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. Applicants have

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amended the claim, as suggested by the Examiner, to correct the deficiency. Therefore, Applicants respectfully request that this objection be withdrawn.

4. Rejections under 35 U.S.C. §112, first paragraph

Claims 74, 78 and 80-83 have been rejected under 35 U.S.C. §112, first paragraph. The Examiner alleges that the application "while being enabling for compounds with L moieties of formulae (i), (ii), (iii) and (v), does not ... provide enablement for compounds with L moieties of formulae (iv) and (vi)." (Page 4, paragraph 9 of the Office action). Specifically, the Examiner states that "there is insufficient guidance as to how to make and use compounds with L moieties of formulae (iv) and (vi)."

In particular, the Examiner cites Applicants' Response filed October 22, 2002 which rebutted the 103(a) *prima facie* obviousness rejection over Pifferi et al. (US 5,120,730) of the July 30, 2002 Office Action. In the October 22, 2002 response, Applicants stated that Applicants' claimed compound of moieties of formulae (iv) and (vi) did not read on Pifferi et al. because the point of attachment between the two moieties is different in the Pifferi et al. compounds from Applicants' claimed invention. The response further stated that "one skilled in the art would have no motivation to prepare the presently claimed subject matter based on the disclosure of Pifferi et al." Applicants further stated that the teachings of Inoue et al. and Nagao et al. taught away from Applicants' invention, and that based upon the teachings of Inoue et al. and Nagao et al., it would not be expected that Applicants' claimed compounds would have biological activity.

The Examiner further alleges that (a) "Applicants have not provided ... data on the activity of the claimed compound", and (b) that the specification "does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed". The Examiner alleges that since Inoue et al. and Nagao et al. teach away from Applicants' point of linkage, and since attaching the linker to a different site on the moiety causes conformational changes in the structure of the compound that affect biological activity which can be "unpredictable", that Applicant's invention in regard to moieties (iv) and (vi) requires undue experimentation.

Applicants respectfully disagree.

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"As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)."

MPEP 2164.01(b)

The specification teaches how to make and use compounds of the invention. (The Examiner herself has already agreed on page 4, paragraph 9 of the January 15, 2003 Office Action that the specification is enabling for compounds with L moieties of formulas (i), (ii), (iii), and (v).) The specification teaches over 700 compounds, of which approximately 180 compounds are heterodimers of formula (iv) or (vi). Detailed step-by-step descriptions of the synthesis of homodimers and heterodimers of formulae (iv) and (vi) are provided in Examples 10, 11-12, and 15-23, and Figures 10 and 15-20.

Additionally, Applicants respectfully submit herewith a Declaration under 37 C.F.R. §1.132 by Dr. Jacqueline Smith which demonstrates that the presently claimed compounds possess *in vitro* inhibitory activity against the L-, N- and T-type calcium channels. Twenty-four compounds, heterodimers or homodimers of formulae (iv), were assayed to determine their ability to inhibit the L-, N- and T-type calcium channels.

As stated in the Dr. Smith's Declaration, the Fluorometric Imaging Plate Reader system (FLIPR) assay used in Applicants' assays is well known as a validated assay for measuring calcium channel activity. See, for example, Denyer et al., *Drug Discovery Today*, 3(7):327-328 (1998) (enclosed as Attachment A). Data results from the in-house T-type calcium channel FLIPR assays were further validated by close correlation of patch clamp assay data and FLIPR data for eight known standard pharmaceutical compounds used as calcium channel blockers.

Representative compounds of the invention were determined to have an average pIC<sub>50</sub> value of 5.5 in the L-type calcium channel assay, 5.2 in the N-type calcium channel assay, and 5.7 in the T-type calcium channel assay. The Declaration further provides, for comparison basis, pIC<sub>50</sub> values determined using the same assay protocols for known therapeutic agents such as mibepradil, flunarizine, and nitrendipine. Thus, the *in vitro* data demonstrates that representative compounds of the invention inhibited the calcium channel at levels equivalent to known therapeutic agents.

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The specification provides general and specific examples of how to make compounds of moieties (iv) and (vi). The attached Declaration demonstrates that representative compounds of the invention have biological activity. The use of such compounds is described on pages 101-102 of the specification. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

5. First Rejection under 35 U.S.C. §102(b)

Claims 74 and 83 have been rejected under 35 U.S.C. §102(b) as being anticipated by Menta et al. (EP 0 266 549). Claims 74 and 83 have been also been rejected under 35 U.S.C. §102(b) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious over either of Devlin et al. (U.S. 4,725,597) or EP 0 122 488.

The Examiner has cited Menta et al. as disclosing a dimeric (bis) fluorophenylpiperazinyl alkane that reads on Applicants' compound of formula L-X-L where both L's are of formula (v). Claim 74 (and thus dependent Claim 83) as amended do not include homodimers of formula (v). Thus, the claims do not read on Menta et al.

Therefore, Applicants respectfully request that the rejection of Claims 74 and 83 based on Menta et al. under 35 U.S.C. §102(b) be withdrawn.

Devlin et al. (U.S. 4,725,597 or EP 0 122 488) discloses a dimeric (bis) chlorophenylpiperazinyl alkane that the Examiner suggests reads on Applicants' compound of formula L-X-L where both L's are of formula (v). Claim 74 (and thus dependent Claim 83) as amended do not recite homodimers of formula (v). Therefore, the claims do not read on Devlin et al.

Since the present claims do not read on Devlin et al., Applicants respectfully request that the rejection of Claims 74 and 83 under 35 U.S.C. §102(b) or alternatively under 35 U.S.C. §103(a) be withdrawn.

In view of the above, Applicants respectfully submit that this application is now in condition for allowance.

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Should there be any remaining issues that can be resolved by telephone, the Examiner is respectfully requested to telephone Jeff Hagenah, an attorney of record at (650) 808-6406, or the undersigned agent at (650) 808-6144.

Respectfully submitted,

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